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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,823	06/01/2005	Akira Kawahara	OMY-0041	7306

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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/516,823	KAWAHARA ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20 and 25-29* is/are rejected.

7)☒ Claim(s) *28 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The preliminary amendment filed on 6/15/06 was not entered because entry of the amendment would have unduly interfered with the preparation of the Office action. See 37 CFR 1.115(b)(2). The amendment was filed nearly a month after Applicant's response electing an invention for prosecution was filed, and the examiner was unaware that any preliminary amendment was forthcoming until after completing the Office action in response to the election. The examiner spent a significant amount of time on the preparation of an Office action before the preliminary amendment was received. Specifically, on the date of receipt of the amendment, the examiner had already completed the Office action (on 6/12/06) and the examiner's supervisor had reviewed, approved, and signed the Office action (on 6/14/06). The case was then counted (on 6/16/06) and prepared for mailing (on 6/21/06). Although the preliminary amendment was filed prior to mailing of the Office action, the examiner and supervisor were unaware that the amendment had been filed until after the Office action was mailed since both the examiner and supervisor had completed all work on the Office action. The date when the preliminary amendment was scanned in and became available for viewing by the examiner and supervisor is not known.

Entry of the preliminary amendment would have required significant additional time on the preparation of the Office action. Entry of the preliminary amendment would have required the examiner to consider and address a number of additional limitations recited in the proposed amendments to claim 20, which would have required an additional search of the patent and non-

patent literature. The examiner would then have had to prepare a new Office action citing additional references and turn the new action in for supervisory review.

2. Applicant's response filed 9/21/06 is acknowledged. Applicant's response does not refer to the preliminary amendment filed on 6/15/06. The reply is responsive to the Office action because the amendments to the claims include markings to show changes relative to the claim set filed 6/1/05 (and not relative to the preliminary amendment of 6/15/06, which has not been entered for the reasons above). In the response, claim 20 has been amended. New claims 25-29 have been added. Claims 1-29 are pending in the application, with claims 1-19 and 21-24 currently withdrawn.

Objections/Rejections Withdrawn

3. The objections to the specification set forth in the previous Office action are withdrawn in response to Applicant's amendments.

4. The rejection of claim 20 under 35 USC 103(a) as being unpatentable over Palmer et al. in view of Dunbar et al. is withdrawn in response to the amendments.

5. The rejection of claim 20 under 35 USC 112, 2nd paragraph set forth in the previous Office action is withdrawn in response to the amendments to claim 20 to recite "collecting" rather than "sampling".

Specification

6. The amendment filed 9/21/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new

matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

On p. 33, line 17 of the marked-up copy of the substitute specification the words "polyclonal antibody" have been changed to "antigen". Applicant's reply did not comment on the change, which changes the meaning of this passage since an antigen is a distinct molecule from a polyclonal antibody.

On p. 35, line 3 of the marked-up copy of the substitute specification the words "Anti-VTG antibody" have been changed to "VTG antigen". This change represents new matter because as originally filed, the specification disclosed an **antibody** coupled to Sepharose, while the specification as amended discloses an **antigen** coupled to Sepharose.

Applicant's reply does not comment on the above changes. Accordingly, the changes are deemed to represent new matter since antibodies and antigens cannot be considered to be interchangeable terms. Applicant is required to cancel the new matter in the reply to this Office Action. If the above amendments represent correction of an obvious error, Applicant may wish to establish this by showing that one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. See MPEP 2163.

Claim Objections

7. Claims 28-29 are objected to because of the following informalities:

The claims should recite "**a**" male frog rather than "**an**" male frog.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 20 and 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 20 recites the steps of "**preparing IgG** from the antiserum" and "**purifying the IgG**". The claim is indefinite because it is unclear exactly what "IgG" is referring to--the IgG fraction of the antiserum, or only to the polyclonal anti-vitellogenin antibodies of the IgG subtype? Furthermore, it is unclear what step(s) are involved in "preparing IgG from the antiserum". It appears that the IgG fraction of the antiserum is being isolated in this step, but the claim later recites "purifying the IgG". It is unclear how these two steps differ.

11. Claim 27 recites that the process of the affinity purification is done "**next to**" the process of the adsorption purification, which is vague and indefinite because the intended meaning of "next to" is not clear in this context. Specifically, it is not clear whether affinity purification occurs "next to" adsorption purification in a spatial or temporal sense. For the purposes of examination, it was assumed that affinity purification is done **after** adsorption purification as depicted in Figure 13 of the specification. If this is consistent with Applicant's intended meaning, the claim should recite "after" or "subsequent to" instead of "next to". If this is not consistent with Applicant's intended meaning, additional clarification is needed.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 20 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawahara et al. ("Quantitative analysis of protein synthesis altered by estrogen in cultured *Xenopus* liver parenchymal cell" (1981) Develop., Growth and Differ. 23, 599-611) in view of Dunbar et al. ("Preparation of Polyclonal Antibodies" (1990) *Methods in Enzymology* **182**, 663-670) and Harlow & Lane ("Antibodies: A Laboratory Manual" (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 283, 285-293 and 313). The Kawahara et al. and Dunbar et al. references are already of record.

Kawahara et al. teach polyclonal antisera specific for frog (*Xenopus laevis*) vitellogenin (see the entire document, especially the abstract and p. 601, "Immunological identification of vitellogenin"). Regarding the limitations of "immunizing a mammal" and "collecting an

antiserum" as recited in claim 20, although Applicant has not established what if any structural differences would accrue to polyclonal antisera produced by such processes, it is noted that the reference teaches that the antisera were in fact produced by such processes using immunized rabbits.

Regarding the limitation of "preparing IgG" from the antiserum, this has been interpreted by the examiner as meaning that the IgG fraction of the antiserum was isolated (see rejection under 112, 2nd paragraph above). This would mean that the claimed polyclonal antiserum would be the IgG fraction. The reference fails to specifically teach isolation of the IgG fraction.

However, Dunbar et al. teach that it is often desirable to partially purify polyclonal antibodies from antiserum prior to use (p. 669-670, "Fractionation of Ig from Serum"). In particular, Dunbar et al. teach DEAE-Sephacel ion-exchange chromatography as well as protein A affinity chromatography as methods to yield the IgG fraction, purified from other immunoglobulin subclasses and most serum proteins.

Therefore, it would have been obvious to one of ordinary skill in the art to isolate the IgG fraction of the polyclonal antibody of Kawahara et al. from antiserum because Dunbar et al. teach that such a step is effective in purifying polyclonal antibodies and that such purification is desirable prior to using the antibodies. It is further asserted that the benefit of using purified reagents was well known in the art at the time of the invention.

Regarding the limitation of "purifying the IgG by an adsorption purification column coupled with blood serum proteins of a male frog", the reference teaches that the prepared antisera were absorbed with normal male sera in order to obtain vitellogenin-specific antisera. The reference fails to specifically state that this process used a "column". Nonetheless, the

reference meets the limitation because in product-by-process claims, a determination of patentability is based on the product itself, and not on the limitations of the steps recited. See MPEP 2113. In this case the use of a "column" to adsorb the polyclonal antisera with normal male sera does not imply any structural difference in the resulting polyclonal antibodies.

Regarding the limitation of "purifying the IgG by...any affinity purification column coupled with a frog vitellogenin", this limitation has been considered in terms of the structure implied by the process of affinity purification in light of the data presented in the specification at Figure 18, where it is seen that specific antibody titers increase after affinity purification. Kawahara et al. fail to specifically teach such an affinity purification process.

Harlow & Lane teach methods of purifying antibodies, including ammonium sulfate fractionation as well as affinity purification on an antigen column (Table 8.3 and p. The reference also teaches that purified antibodies are desirable for a number of reasons, in that they may lower the background in some assays (p. 288). Also, when labeled antibodies are used to detect antigens directly, the antibodies must be purified first. The reference teaches that affinity purification using an antigen affinity column, in which the antigen is bound covalently to a solid support, can be used for producing highly pure and specific polyclonal antibodies (p. 293 and 313). The reference further teaches that affinity purification on an antigen column has a unique ability to isolate specific antibodies from a mixed pool.

Therefore, it would have been further obvious to one of ordinary skill in the art at the time of the invention to purify the polyclonal antibodies of Kawahara et al. on an antigen (i.e. vitellogenin) affinity column in order to obtain a highly pure and specific preparation.

With respect to claims 25-26, which refer to the adsorption and affinity purification processes addressed above, are not found to further limit the claimed product because they do not clearly require any additional steps to be performed. See MPEP 2111.04. The recited "wherein" clauses ("wherein antibodies to proteins in the blood serum of the male frog are eliminated by the process of the adsorption purification" and "wherein antibodies to the frog vitellogenin are bonded to the affinity purification column by the process of the affinity purification") do not recite any additional active method steps, but simply state a characterization or conclusion of the results of those steps. Therefore, the "wherein" clauses are not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

With respect to claim 27, this claim has been interpreted as meaning that affinity purification is performed after adsorption purification. The reference(s) meet the claim because no structural difference in the resulting polyclonal antibodies can be envisaged as a result of the order in which the two purification steps are performed.

With respect to claim 28, Applicant has not provided any evidence showing that polyclonal antibodies elicited against vitellogenin induced in a *male* frog would be structurally

different than polyclonal antibodies elicited against vitellogenin induced in a *female* frog as in Kawahara et al.

Similarly, with respect to claim 29, Applicant has not provided any evidence showing that polyclonal antibodies purified by use of an affinity purification column coupled to vitellogenin produced by a male frog would be structurally different than those purified by use of a column coupled to vitellogenin produced by a female frog.

15. Claims 20 and 25-29 rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. ("*In Vitro* Translation and Estradiol-17β Induction of *Xenopus laevis* Vitellogenin Messenger RNA" *The Journal of Biological Chemistry* Vol. 251 No. 10, p. 3105-3111, 1976) in view of Kawahara et al. and Harlow & Lane ("Antibodies: A Laboratory Manual" (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 283, 285-293 and 313).

See the rejection above for further elaboration regarding claim interpretation.

Shapiro et al. teach polyclonal antibodies specific for frog (*Xenopus laevis*) vitellogenin (see especially the abstract and p. 3105-3106, "Methods" and p. 3106, right column, "Characterization of Antibodies"). Although the reference does not use the term "polyclonal" to describe the antibodies, the process set forth in the reference would be immediately envisaged by one skilled in the art as one producing polyclonal, rather than monoclonal, antibodies. The reference teaches that the antibodies were produced by immunizing rabbits with purified vitellogenin and isolating the antisera (see in particular p. 3106, the left column). The reference further teaches preparing the IgG (γ-globulin) fraction by ammonium sulfate fractionation (p. 3106, "Preparation of Antibodies").

Shapiro et al. fail to specifically teach that the polyclonal antibodies were purified by adsorption and affinity purification.

Kawahara et al. (discussed above), teach production of polyclonal antibodies against vitellogenin, in which the prepared antibodies are subsequently absorbed with normal male frog serum in order to obtain antibodies specific for vitellogenin (p. 601, "Immunological identification of vitellogenin").

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to adsorb normal male frog serum (and therefore the proteins contained therein) with the polyclonal antibody preparation of Shapiro et al. in order to isolate those antibodies in the preparation that are specific for vitellogenin as taught by Kawahara et al. The use of a "column" during the adsorption process is not found to further limit the patentability of the claimed product.

Harlow & Lane (discussed above) teach methods of purifying antibodies, including ammonium sulfate fractionation as well as affinity purification on an antigen column (Table 8.3 and p. The reference also teaches that purified antibodies are desirable for a number of reasons, in that they may lower the background in some assays (p. 288). Also, when labeled antibodies are used to detect antigens directly, the antibodies must be purified first. The reference teaches that ammonium sulfate fractionation alone is not recommended as a single step, since it still yields impure antibody, and that it must be coupled with other techniques (Table 8.3 at p. 292). The reference also teaches affinity purification using an antigen affinity column, in which the antigen is bound covalently to a solid support, which can be used for producing highly pure and specific polyclonal antibodies (p. 293 and 313). The reference further teaches that affinity

purification on an antigen column has a unique ability to isolate specific antibodies from a mixed pool.

Therefore, it would have been further obvious to one of ordinary skill in the art at the time of the invention to purify the polyclonal antibodies of Shapiro et al. and Kawahara et al. on an antigen (i.e. vitellogenin) affinity column in order to obtain a highly pure and specific preparation, as taught by Harlow & Lane, since ammonium sulfate fractionation alone (as was done in Shapiro et al.) is not recommended as a single step for purifying antibodies, but must be coupled with other purification techniques.

With respect to claims 25-27, the recited limitations have not been given weight in construing the claims, as discussed above.

With respect to claims 28-29, although Applicant has not established what if any structural differences would accrue to polyclonal antibodies produced by the recited processes, it is noted that Shapiro et al. teach that the antibodies were produced using vitellogenin antigen produced in male frogs induced with estradiol-17β (p. 3105-3106). Since it is this vitellogenin preparation that was the antigen in Shapiro et al., it would have been obvious to also employ it as the *antigen* affinity column since Harlow & Lane teach that by coupling the antigen to a solid support, highly pure antibodies can be obtained.

Response to Arguments

16. Applicant's arguments filed 9/21/06 have been fully considered.

17. With respect to the rejection of claim 20 as being unpatentable over Palmer et al., Applicant's arguments have been fully considered but are moot in light of the new grounds of rejection necessitated by the claim amendments.

Conclusion

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

19. Berridge et al. "Characterization of Polysomes from *Xenopus* Liver Synthesizing Vitellogenin and Translation of Vitellogenin and Albumin Messenger *RNA's in vitro*" Eur. J. Biochem. 62, 161-171 (1976).

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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